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Association of Hypercholesterolemia with Alzheimer's Disease Pathology and Cerebral Amyloid Angiopathy

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Abstract

Background: Animal studies have shown that diet-induced hypercholesterolemia (HC) increases amyloid-β (Aβ) accumulation and accelerates Alzheimer's disease (AD) pathology. However, the association of HC with AD in human studies has not been consistently established.

Objective: We aimed to investigate the relationship between HC and risk of AD neuropathology in a large national sample with autopsies.

Methods: This study used neuropathological and clinical data from 3,508 subjects from the National Alzheimer's Coordinating Center (NACC) who underwent autopsies from 2005 to 2017. Demographic and clinical characteristics, as well as neuropathological outcomes were compared between subjects with and without HC. Associations between HC and AD neuropathology were examined by multivariate ordinal logistic regressions adjusting for potential confounders.

Results: HC was not associated with any AD neuropathology in a model only adjusting for demographic variables. However, HC was significantly associated with higher CERAD neuritic and diffuse plaque burden, higher Braak stage, and more severe cerebral amyloid angiopathy when analyzed in a multivariate model controlling for comorbidities. Additional adjusting for cerebrovascular conditions did not diminish these associations. The association between HC and increased risk of neuritic plaques weakened but remained significant even after controlling for ApoE genotype.

Conclusion: This study suggested that HC was associated with increased severity of AD pathology, which could only be partially accounted for by ApoE genotype. The associations were not mediated by cerebrovascular conditions.

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Keywords

Alzheimer's disease; ApoE genotype; cerebral amyloid angiopathy; hypercholesterolemia; neuropathology

INTRODUCTION

More than 25 million people lived with dementia worldwide, most of whom are suffering from Alzheimer's disease (AD) [1]. The long duration of illness in a state of disability and dependence makes it a significant burden to public health and health care system [2]. Epidemiological studies have identified multiple modifiable risk and protective factors. Among them, vascular risk factors are most consistently reported, including hypertension [3], type II diabetes [4], and cerebrovascular disease (CVD) [5].

The hallmark pathological changes in AD patients' brain tissue involve amyloid-β (Aβ) peptide deposition and tau hyperphosphorylation [6]. Aβ production and clearance are regulated in part by cholesterol pathway. The strongest common genetic risk factor, a variant of ApoE, is an apolipoprotein that plays an essential role in cholesterol metabolism. Altered cholesterol metabolism may induce a change in membrane properties, leading to an alteration in Aβ production [7]. Cholesterol oxidation products, oxysterols, are suggested to be the link between altered cholesterol metabolism in the brain and Aβ aggregation [8].

Animal studies have shown that diet-induced hypercholesterolemia (HC) increases Aβ accumulation and accelerates AD pathology in rabbit brains [9] and in a transgenic mouse model [10, 11]. The authors therefore proposed that dietary control could be used to modify the risk of AD. Two statins have shown a pleiotrophic effect to achieve cognitive improvement in transgenic AD mouse model, without affecting serum lipid levels [12]. However, the association of HC with AD in human studies has not been consistently established. Elevated serum total cholesterol in midlife [13] and in the elderly [14] is found to be associated with an increased risk of AD. However, a community-based cohort study [15] did not find an association between serum total cholesterol and subsequent incidence of AD. Furthermore, a recent meta-analysis on the association between serum cholesterol and dementia has identified significant gaps in the literature regarding HC and AD risk [16]. Some studies suggest that dyslipidemia increases the risk of plaque-type AD pathology, but not the densities of neurofibrillary tangles (NFT) [17, 18]. But other lines of evidence do not support this association [19, 20].

In this study, we use the National Alzheimer's Coordinating Center (NACC) database to investigate the relationship between HC and AD neuropathologic outcomes, including neuritic plaques (NP), NFTs, diffuse plaques (DP), and cerebral amyloid angiopathy (CAA). We further examine whether vascular pathology was a mediator between HC and AD neuropathology.

METHODS

Data sources and study populations

The National Alzheimer's Coordinating Center (NACC) database is the largest resource of standardized clinical and neuropathological data related to AD in the U.S. NACC collects data from approximately 32 past and present Alzheimer's Disease Centers (ADCs) across the United States since the beginning of the program in 1984. Data collection was fully standardized across centers in 2005 with the development of the Uniform Data Set [21]. Data collected between September 2005 and February 2017 were used in this analysis.

We used the following demographic variables: age at death, race, sex, and education. Self-or-caregiver-reported subject medical history was longitudinally collected from initial visit and each annual follow-up visit at ADCs. A series of medical conditions were dichotomized as present or absent and were controlled for as potential confounders, including HC, stroke, transient ischemic attack, diabetes, cardiovascular disease, and hyper-tension. History of cardiovascular disease was coded as present or absent, by combining 9 types of cardiovascular disease recorded in the UDS form, including heart attack/cardiac arrest, atrial fibrillation, angioplasty/endarterectomy/stent, cardiac bypass procedure, pacemaker and/or defibrillator, congestive heart failure, angina, heart valve replacement or repair, and other cardiovascular disease. Presence of any one or more of these was coded as positive cardiovascular disease. In addition, self or caregiver reported use of lipid lowering medication was collected from each visit. ApoE genotype was available for 87.5% of the subjects in our study and coded as number of ε4 alleles (0, 1, or 2).

Assessment of neuropathologic measures

Neuropathologic data were obtained from NACC's standardized Neuropathology Form [21, 22]. Consortium to Establish a Registry for Alzheimer's Disease (CERAD) stages of Aβ NP densities were recorded as none, sparse, moderate, or frequent [23]. Braak scores for neurofibrillary degeneration were used with stage 0 indicating no degeneration and stage VI indicating NFTs found throughout the neocortex [24]. CAA stage was classified as none, mild, moderate, and severe. AD neuropathologic change (ADNC) and Thal phase for amyloid plaques by immunohistochemistry were included in the Neuropathology Form after 2014. These data were excluded from this study due to limited sample size.

To describe the severity of cerebrovascular conditions, we dichotomized 6 groups of neuropathology as present or absent, including large artery infarcts or lacunes (old/acute/subacute), hemorrhages (old/acute/subacute), microinfarcts (old/acute/subacute), subcortical arteriosclerotic leukoencephalopathy, atherosclerosis of the Circle of Willis and Arteriolosclerosis [25]. Acute and old/subacute CVD neuropathology were evaluated separately in the most recent version of the Neuropathology Form, but together in older versions. We combined these categories in order to use all data available. Infarcts observed grossly and lacunes were grouped together according to the newest version. Subjects were scored 0–6 by the numbers of CVD neuropathology groups observed in the brain.

Statistical analyses

Demographic, clinical, and neuropathologic characteristics were compared between subjects with or without HC using Pearson chi-square tests for unordered categorical variables, *t*-tests for continuous variables, and Wilcoxon-Mann-Whitney tests for ordinal variables.

We used proportional odds ordinal regression model with generalized estimating equations to account for ADC clustering to analyze the association between HC status and each of the five neuropathology outcomes, namely, CVD score, Braak stage, CERAD NP and DP density, and CAA severity. We created four separate models. In the first multivariable model, we only controlled for age at death, year of education, sex, and race. In the second model, we additionally controlled for relevant comorbidities including hypertension, cardiovascular disease, diabetes, history of stroke or transient ischemic attack, each as a separate variable. An indicator for ApoE ε4 carrier status was included in the third model, which was limited to the subjects that had ApoE ε4 information available. This model examined whether ApoE ε4 is a mediator in the relationship between HC and severity of AD neuropathology. Lastly, CVD score was included in the fourth model to investigate whether CVD is a mediator in the relationship between HC and pathology burden. Significance was defined as p value < 0.05.

RESULTS

Total of 3,508 subjects were included in the analysis, who underwent brain autopsies and had non-missing Braak, CERAD, CAA, and CVD staging scores. Demographic and clinical characteristics are summarized and compared by subjects' HC status in Table 1. There were no significant differences in age at death, race, and education levels between subjects with and without HC. There were more males in subjects with HC than those without. Subjects with a history of HC were more likely to carry one or more ApoE ε4 alleles and to have other medical conditions, such as cardiovascular disease, hypertension, diabetes, stroke, and transient ischemic attack.

In the unadjusted between-group comparisons subjects with HC had higher CERAD DP density scores and more severe CAA (Table 2) than those without HC. Subjects with HC did not differ significantly in CVD scores, CERAD NP score, or Braak score for NFTs from those without HC (Table 2).

Table 3 summarizes the results of our multivariate models. In Model 1 where we adjusted for age at death, sex, race, and education only, HC was not significantly associated with any of the neuropathologic outcomes. There were significant associations between HC and all AD neuropathology outcomes after additionally adjusting for comorbidities (Model 2). Specifically, having a history of HC was associated with a 21%, 26%, 32%, and 26% higher odds of having higher Braak (OR = 1.21 [95% CI: 1.04–1.43]), higher CERAD NP density score (OR = 1.26 [1.08–1.47]), higher CERAD DP density score (OR = 1.32 [1.06–1.64]), and more severe CAA (OR = 1.26 [1.08–1.47]), respectively (Model 2). HC was also associated with lower CVD score with borderline significance (p value = 0.0436) (Model 2).

We investigated whether the association between HC and AD neuropathology was mediated by ApoE ε4 genotype or cerebrovascular conditions (Models 3 and 4, respectively). We found that ApoE ε4 genotype was significantly associated with all neuropathologic outcomes. After controlling for ApoE ε4 allele carrier status, the associations between HC, CVD, Braak stage, CERAD DP, and CAA became nonsignificant. The association between HC and CERAD NP was reduced, but remained significant. The associations between HC and all four pathologic indices, Braak stage, CERAD NP and DP density. and CAA, all remained significant after adjusting for CVD score in the model (Model 4). We further evaluated the effect of lipid lowering medication on the connection between HC and AD pathology. Lipid lowering medication itself was not significantly associated with any pathological outcomes evaluated. The associations between HC and four AD pathologic indices all remained significant after adjusting for lipid lowering medication use (Model 5).

We found that ApoE ε4 genotype was significantly associated with all neuropathologic outcomes. We further examined the association between ApoE ε4 genotype and NFTs in the subjects with no or sparse amyloid pathology (CERAD NP density score = 0 or 1) and the relationship remained significant (Table 4).

DISCUSSION

In this large autopsy sample, we found that HC was associated with increased severity of neuropathology including NFTs, NP and DP densities, and CAA. These associations were independent of neuropathological CVD severity score and cannot be completely explained by ApoE ε4 carrier status.

Our findings were in general consistent with the Honolulu-Asia Aging Study (N = 218) [26], which reported a strong linear association for increasing midlife and late-life HDL cholesterol and an increasing number of neocortical NPs and NFTs. Another retrospective study (N = 140) [27] suggested that serum hypercholesterolemia was associated with AD amyloid pathology in subjects 40–55 years of age. This study only investigated amyloid pathology. The Hisayama Study [17] suggested that dyslipidemia increased the risk of plaque-type AD pathology but found no relationship between any lipid profile and NFTs. The absence of association between the lipid profiles and NFTs might be due to limited sample size (N = 147). Compared to previous studies, our study has the advantage of large sample size (N = 3508). We investigated a broader range of AD pathology indices, including NPs, DPs, NFTs, and CAA. Instead of measuring cholesterol level at a certain time point, we collected history of HC as an indicator of the potential risk. We believed that lifetime history would be a more stable and reliable measure compared to a single-time-point measurement. This study discovered that hypercholesterolemia was associated with increased risk of both amyloid and tau pathology, which is consistent with the majority of the animal and *in vitro* studies [10, 11].

An important innovation of our study was comparison of models with and without CVD scores. Based on these models we are able to conclude that CVD is not a mediator in the association of HC with AD pathology. Concurrent CVD is a common neuropathological finding in AD patients and is believed to contribute to AD neuropathological changes [28].

Therefore, vascular risk factors, such as HC, might have increased the risk of AD through vascular mechanism [29]. Our study demonstrated that HC is associated with AD neuropathological changes independent of CVD burden.

Observational studies have shown conflicting results on the effect of statin use on AD [30]. In 2012, the United States Food and Drug Administration issued a warning of statin drugs labeling regarding potential adverse effects on cognition [31]. Randomized controlled trials that assessed the effects of statin use on cognition did not support a causal preventative effect [30] or adverse effect [32]. In our study, we found that the use of lipid lowering medications did not change the association between HC and AD neuropathology.

Since ApoE ε4 plays a crucial role in cholesterol metabolism and transport in the brain, and is also a strong genetic risk factor for AD pathogenesis, we examined the relationship between ApoE ε4 genotype, HC, and AD pathology by comparing two multivariate models (Model 2 and Model 3). The associations between HC and DP pathology or CAA were no longer significant after adjustment for ApoE ε4 genotype, yet the association with NP burden remained significant suggesting that ApoE ε4 genotype mediates the relationship of HC with vascular amyloid and early diffuse amyloid pathology but not so much the relationship with the mature plaques. Other genetic risk factors for AD, such as HMGR gene, which encodes the primary regulator of cholesterol synthesis, might be the additional linkage between abnormal cholesterol level and AD pathogenesis [33].

Extensive evidence supports that ApoE affects the risk of AD mainly through Aβ cascade [34, 35]. It was reported that ApoE genotype was only associated with tau pathology in the presence of Aβ, which was evaluated by immunohistochemistry [5]. Interestingly, we found a significant ApoE ε4 association with higher NFT burden even in subjects with no or sparse amyloid pathology (CERAD NP score = 0 or 1) (Table 4). The discrepancy between our results and the previous report may reflect the difference in methods for staging Aβ pathology. Although both methods quantify Aβ pathology, there is no consistent relationship between CERAD score system and immunohistochemical staining of Aβ, such as Thal Aβ phase [36]. In addition, the study by Farfel et al. included smaller number of subjects without Aβ compared to our current study (N = 152 compared to N = 1225) [5] and perhaps limited power to identify an association between ApoE ε4 genotype and tangles in subgroups stratified by Aβ. Based on our findings in Models 2 and 3, we conclude that the association between HC and NFTs is to a significant extent mediated by ApoE ε4 genotype.

Our study also had several limitations. First, the semiquantitative assessment of NPs and NFTs could affect the accuracy of the results. Second, we used self or caregiver reported medical history for hypercholesterolemia in our analysis, which may be subject to recall bias. Medication use was also collected from self or caregiver report and we did not consider duration or adherence of medication use. In addition, cholesterol levels were not available in this data set.

In conclusion, our study found that history of hypercholesterolemia, independent of its impact on cerebrovascular conditions, is associated with increased severity of AD pathology.

In addition to the well-established ApoE ε4 effect on Aβ pathology, this study found that ApoE ε4 is associated with increased NFT pathology in the absence of Aβ pathology.

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Table 1

Comparisons of demographic and clinical characteristics by history of hypercholesterolemia status

Characteristics	With HC		Without HC		*p**
	N	Mean (±SD) or No. (%)	N	Mean (±SD) or No. (%)	
Age at death, y	1901	80.6 (±10.6)	1607	80.1 (±13)	0.2230
Male	1901	1082 (56.9%)	1607	812 (50.5%)	0.0002
Race: Caucasian	1895	1793 (94.6%)	1597	1522 (95.3%)	0.6378
African American		71 (3.8%)		51 (3.2%)	
Years of education	1879	15.3 (±3.2)	1578	15.1 (±3.2)	0.2296
Cardiovascular disease	1901	921 (48.4%)	1607	489 (30.4%)	<.0001
Hypertension	1901	1316 (69.2%)	1607	700 (43.6%)	<.0001
Diabetes	1900	318 (16.7%)	1607	102 (6.3%)	<.0001
Stroke	1898	231 (12.2%)	1600	137 (8.6%)	0.0005
Transient ischemic attack	1885	200 (10.6%)	1598	122 (7.6%)	0.0025
Lipid lowering medication use	1901	1083 (57%)	1576	80 (5.1%)	<0.0001
ApoE ε4 carrier	1665		1403		
No ε4 alleles		899 (54%)		826 (58.9%)	
1 ε4 allele		616 (37%)		480 (34.2%)	0.0034
2 ε4 alleles		150 (9%)		97 (6.9%)	

HC, hypercholesterolemia; SD, standard deviation.

*p values were obtained from Pearson chi-square test, t-test, or Wilcoxon-Mann-Whiney test as appropriate.

Table 2

Comparisons of neuropathologic measures by hypercholesterolemia status

Neuropathology	levels	With HC (*N* = 1901) no. (%)	Without HC (*N* = 1607) no. (%)	*p**
Cerebrovascular score	0	45 (2.4%)	34 (2.1%)	0.7953
	1	210 (11%)	211 (13.1%)	
	2	517 (27.2%)	416 (25.9%)	
	3	641 (33.7%)	528 (32.9%)	
	4	353 (18.6%)	285 (17.7%)	
	5	119 (6.3%)	114 (7.1%)	
	6	16 (0.8%)	19 (1.2%)	
Braak stage for neurofibrillary degeneration	Stage 0	120 (6.3%)	135 (8.4%)	0.3510
	Stage I/II	381 (20%)	307 (19.1%)	
	Stage III/IV	424 (22.3%)	354 (22.1%)	
	Stage V/VI	976 (51.3%)	811 (50.5%)	
CERAD score for density of neuritic plaques	None	404 (21.3%)	395 (24.6%)	0.1431
	Sparse	240 (12.6%)	186 (11.6%)	
	Moderate	355 (18.7%)	284 (17.7%)	
	Frequent	902 (47.4%)	742 (46.2%)	
CERAD semi-quantitative score for diffuse plaques	None	277 (14.6%)	287 (17.9%)	0.0079
	Sparse	216 (11.4%)	198 (12.3%)	
	Moderate	324 (17%)	263 (16.4%)	
	Frequent	1084 (57%)	859 (53.5%)	
Cerebral amyloid angiopathy	None	738 (38.8%)	677 (42.1%)	0.0237
	Mild	571 (30%)	481 (29.9%)	
	Moderate	401 (21.1%)	302 (18.8%)	
	Severe	191 (10%)	147 (9.1%)	

HC, hypercholesterolemia; CERAD: Consortium to Establish a Registry for Alzheimer's Disease.

* *p* values were obtained from Wilcoxon-Mann-Whiney test.

Table 3

Multivariate analysis of association between HC and AD/CVD neuropathology

	Odds Ratio (*p*)				
Neuropathology outcome	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Cerebrovascular score	0.97 (0.6694)	0.86 (0.0436)	0.88 (0.112)		0.83 (0.0653)
Braak stage for neurofibrillary degeneration	1.05 (0.4941)	1.21 (0.0173)	1.13 (0.1763)	1.23 (0.0172)	1.22 (0.0339)
CERAD score for density of neuritic plaques	1.09 (0.3078)	1.26 (0.0037)	1.19 (0.0269)	1.28 (0.0027)	1.26 (0.0183)
CERAD semi-quantitative score for diffuse plaques	1.17 (0.1451)	1.32 (0.014)	1.24 (0.0525)	1.32 (0.0123)	1.31 (0.0296)
Cerebral amyloid angiopathy	1.13 (0.104)	1.26 (0.0039)	1.15 (0.0539)	1.28 (0.0025)	1.25 (0.0128)

HC, hypercholesterolemia; CERAD: Consortium to Establish a Registry for Alzheimer's Disease. Model 1 was adjusted for age at death, sex, race, and education. Model 2 was adjusted for age at death, sex, race, education, hypertension, cardiovascular disease, diabetes, stroke, and transient ischemic attack. Model 3 was adjusted for ApoE ε4 alleles in addition to the same variables in Model 2. Model 4 was adjusted for cerebrovascular score in addition to the same variables in Model 2. Model 5 was adjusted for lipid lowing medication use in addition to the same variables in Model 2.

Table 4

Multivariate analysis of association between *APOE* and Braak stage for neurofibrillary degeneration

	Odds Ratio (*p*)	
	Total (*N* = 3068)	**No or sparse NPs (*N* = 1225)**
1 copy of ApoE ε4	3.39 (<0.0001)	2.39 (<0.0001)
2 copies of ApoE ε4	10.04 (<0.0001)	9.34 (0.0006)

Models were adjusted for age at death, sex, race, and education.